proof now rests with those advocating use of these drugs for therapy of postmenopausal conditions. Until there can be presented more convincing evidence that estrogens are *not* carcinogenic, it is my clear and unequivocal conclusion that the clinical community should and must withhold such therapy from all but the most severely ill patients.

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Dr. Gordan Replies

TO THE EDITOR: Dr. Stephen Brown's thoughtful critique gives me the opportunity to expand my "somewhat hasty dismissal of the notion that estrogen therapy in postmenopausal women causes uterine cancer." I share Dr. Brown's concern. Certainly no physician takes any cancer lightly. The reader may judge whether I have dismissed this important matter hastily. If one accepts at face value, as Dr. Brown does, the reports of Ziel and Finkle* and Smith and co-workers,* and the subsequent report of Mack and co-workers,* one would have to decide whether the risks of endometrial cancer outweigh the established certainty of fractures of the vertebrae, wrists and hips with their attendant morbidity and mortality in estrogen-deficient ethnically predisposed women (postmenopausal or oophorectomized). It is not correct that endometrial cancer is highly lethal; the type of cancer associated with estrogen therapy is most likely to be detected early and at a curable stage, probably because of proper examination for uterine bleeding. In the study of Smith and associates, 95 percent of the estrogen-associated cancers were Stages 0 or 1 (atypical adenomatous hyperplasia or carcinoma *in situ)*—which would not be recorded as cancers in the San Francisco Bay area Cancer Registry.[1] Only one was associated with deep myometrial invasion. In contrast, 25 percent of the cancers not associated with estrogen were in the higher stages of

*References 3-5 above.

malignancy and more deeply invasive. It should be noted that mortality figures from the National Center for Health Statistics show a constant low mortality from this cause accounting for 1.4 percent of all cancers in women for the period 1968 through 1974.[2] There were 2,252 deaths from corpus cancer in the United States in 1974. A quarter of these in blacks were myometrial sarcomas. I know no evidence that hysterectomy increased in this period; the report of Bunker in 1970[3] suggests that the major increase preceded this period. Brown's interpretation of Cramer's data* is opposite that of Cramer himself who concludes that endometrial cancer mortality is declining.

I cannot agree that the three retrospective case-control studies prove that estrogens cause cancer. I consider all three erroneous and illogical for the following reasons:

- Not all the so-called "cancers" were cancers. Smith's 95 percent Stage 0 and 1 cases are cited above. Ziel's series was subsequently reviewed by three pathologists headed by Arthur Hertig.[4] Ziel had based his data on 94 "cancers" but only 66 were accepted by all three pathologists and 76 by two. As far as I can ascertain, Mack's cases have not been subjected to extramural review. The difficulties of differentiating estrogen-induced hyperplasia from early carcinoma are well known and have recently been reviewed in connection with the present problem by Kistner.[5]

- Many of the women (28 percent of Ziel's series) received estrogen only in the three-year period preceding diagnosis. Since endometrial cancer usually developed over many years,[6] how many of these women were given estrogen to regulate perimenopausal bleeding actually due to preexisting carcinoma?

- The "cases" and "controls" were not similarly examined. It is not surprising that women subjected to curettage have more endometrial abnormalities read as cancer than unexamined women.

- In Smith's study the "controls" were women with other gynecologic carcinomas, two thirds of them carcinoma of the cervix. Since this disease occurs most commonly in the most neglected socioeconomic class while carcinoma of the endometrium is most common in the affluent, it is not surprising that estrogen administration was less frequent in poor than in rich women.

- Ascertainment bias is probable, for example, in Ziel's study where only cases reported to the Tumor Registry were included. But not all cases were reported to the Registry. It is not surprising that women who see doctors more often and are therefore more likely to be reported to the registry receive estrogen more frequently than women who do not. Exclusions of hysterectomized controls undoubtedly lowers estimation of control incidence of estrogen therapy.

- The logic is bothersome: How can one apply random statistics to a subset of patients with particular socioeconomic and medical characteristics?

- Even if increased association is established it does not necessarily prove cause. Increased association could even be spurious. In a witty, heuristic presentation of this important epidemiologic consideration, the great statistician Jerzy Neyman describes a strong association between the ratio of storks to women in 54 counties in California and the birth rate.[7] This is clearly a spurious correlation; it does not prove that storks bring babies.

Weiss describes increased "incidence" of endometrial cancer in eight selected Cancer Registries. I put incidence in quotation marks since the number of women at risk is not known. The last census with such detailed information was taken in 1970. Subsequent migratory population shifts and public support for medical care undoubtedly have altered the population base, certainly in California. Similar increases in incidence of endometrial cancer are reported from Norway[8] where estrogen use is rare, and from Czechoslovakia[9] where estrogen use is reportedly nil. Obviously, increased detected incidence can result from extension of medical care to previously neglected population, from better investigation of uterine bleeding and from changing diagnostic criteria to increased borderline histologic changes —all of which have probably occurred in the United States in the past decade. The registries Weiss selected used widely varying diagnostic criteria: Connecticut includes *in situ and* noninvasive tumors; the San Francisco Bay area registry does not. Increased estrogen use is certainly not the cause of the increased incidence of endometrial cancer noted in Norway and Czechoslovakia.

I am sorry that Dr. Brown doesn't like the studies of Dunn and Bradbury† or Pacheo and Kempers;† Greenberg and I[10] consider them better

*Reference 8 above.

†References 13, 14 above.

controlled than the three he cites. Estrogen use was not uncommon at the time of these studies: 28 percent of these indigent women studied at the University of Iowa a decade ago had received estrogens. Dunn and Bradbury anticipated Dr. Brown's criticism by excluding women bleeding from hyperplastic endometria. In answer to Dr. Brown's question, the incidence of corpus cancer in both the Second and Third National Cancer Surveys peaked at the postmenopausal age of 62 and was constant at 80 per 100,000 women. My 220 estrogen-treated women averaged 62 years of age at the start of treatment and were treated for 1,868 patient years. Random incidence therefore would have produced $\frac{80}{100,000} \times 1,868 = 1.5$ cases: "between 1 and 2 cases."

We detected three cases of carcinoma of the endometrium, all *in situ* and all found because of curettage for breakthrough bleeding. I do not claim that 220 cases are adequate for epidemiology of uncommon cancers. They sufficed for fracture incidence, the prime purpose of this study, since osteoporotic women average 50 to 70 fractures per 1,000 patient years.[11,12] My patients who received full replacement doses of estrogen sustained only three fractures per 1,000 patient years.[13]

Of course estrogens are carcinogens, at least when given continuously in large doses to susceptible strains. Estrogens are carcinogens in exactly the same sense that digitalis and vitamin D are lethal poisons. The young women with clear cell carcinoma of the vagina to whom Dr. Brown refers had been exposed to very large doses of nonsteroidal estrogens prenatally. The main thrust of my paper is that surprisingly small doses of estrogens which rarely produce endometrial hyperplasia or bleeding suffice to prevent postmenopausal bone loss. Very recent data[14,15] show that 20 to 25 μg per day of mestranol or 0.625 mg per day of conjugated estrogens are adequate for this purpose. Since postmenopausal bone loss, which leads to fractures of the vertebrae, wrists and hips in postmenopausal or oophorectomized women can be prevented, epidemiologists and other public health workers could help to stamp out preventable crippling and sometimes fatal fractures in ethnically predisposed women. We need accurate data on how many elderly women die of hip fractures, not presently recorded as a cause of death in vital statistics, and whether estrogen prophylaxis can prevent these fractures and deaths. Properly carried out retrospective studies have produced extremely important information, for example, 90 percent of the 90,000 lung cancer deaths this year will occur in smokers. Retrospective studies are notoriously difficult to control and have brought forth some associations which were subsequently refuted—for instance, reserpine and breast cancer, coffee and myocardial infarcts. Horwitz and Feinstein note that many retrospective studies fail to meet the criteria of common sense and logic.[16] It is a source of great concern and a potential hazard to American and international health that public policy has been based on such studies. Perhaps the one benefit of the present concern will be better examination of estrogen-treated women. In evaluating any therapy, it is essential to weigh risks versus benefits. But the current controversy is not simply a matter of trading off the risk of endometrial cancer for that of osteoporosis. In my carefully considered opinion, it is now established that the menopause or oophorectomy leads to bone loss. I do not believe it has been shown that properly administered estrogens cause cancer. A large number of prospective studies show that they do not.

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